UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 15-2606 (RBK)(JS)**

PLAINTIFFS' BRIEF IN SUPPORT OF DAUBERT MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT JERROLD TURNER, M.D.

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PRELIMINARY STATEMENT

Dr. Jerrold Turner contends that there is no causal association between Olmesartan and sprue-like enteropathy, despite overwhelming evidence to the contrary, including:

- **The FDA required a warning to be added to the Olmesartan drugs and issued a Drug Safety Communication to health care professionals and patients informing them that Olmesartan *can cause* intestinal problems known as sprue-like enteropathy.** Dr. Turner's opinion directly contradicts the FDA's pharmacovigilance and medical review, which included a review and analysis of the medical literature, adverse event reports, rechallenge data, the Mini-Sentinel and CMS Medicare Data Results, as well as a review of potential mechanisms.

- **There is no peer-reviewed article that concludes there is not a causal association between Olmesartan and sprue-like enteropathy.**

- **The only randomized-controlled study relied on by the defense experts to deny a causal relationship is ROADMAP, which was not adequately powered to evaluate the causal relationship and was designed with no gastrointestinal endpoints.**

- **The defense experts admit that the medical literature is sufficient for clinicians to diagnose sprue-like enteropathy due to Olmesartan in a patient, and permanently withdraw Olmesartan.**

- **The type of clinical data sought by the defense experts does not exist because it would not be feasible to construct a randomized, controlled study of the question, and the medical literature establishes that it would be unethical to subject patients to controlled rechallenges.**

- **The defense experts have no clinical experience with sprue-like enteropathy.** In fact, Dr. Turner learned of the existence of this syndrome only after being contacted by defense counsel.

- **None of the defense expert causation opinions are published or peer-reviewed.**

Dr. Turner applied no methodology to reach the net opinion that Olmesartan does not cause sprue like enteropathy, Olmesartan induced enteropathy, or Olmesartan associated enteropathy (interchangeably referred to as "SLE," "OIE," or "OAE") in any patients, based solely on his review of selected literature, a conclusion that is not stated in any peer-reviewed publication.

This outlier opinion is the product of Dr. Turner's refusal to accord significance to any study that was not controlled and randomized. As a result, he discounted or rejected all positive evidence he reviewed that was not generated by a controlled, randomized trial. The ultimate net opinion yielded by this unscientific analysis cloaked in the terminology of science is a superficial net opinion at best, essentially reduced to scoring a selected subset of articles based on how each study was performed, in order to reach the predetermined conclusion that there are not enough "high level" studies proving causation to conclude that Olmesartan causes SLE.

In fact, Dr. Turner admits that it is possible Olmesartan can cause enteropathy, admits that positive dechallenges and rechallenges reported in the literature weigh in support of the opinion that Olmesartan causes OIE, and even admits that Olmesartan is the likely cause of the villous atrophy, severe diarrhea, weight loss, and hospitalizations described in certain case reports. Dr. Turner's net opinion, based upon a personal rather than generally accepted standard, would be misleading to a jury as it purports to be a rigorous medical analysis as to causation, but is merely a conclusion-driven selection process.

STATEMENT OF FACTS

1. Dr. Turner's Outlier Opinion.

Dr. Turner admitted that there is no article in the peer-reviewed literature that reaches the conclusion that Olmesartan does not cause Olmesartan-associated enteropathy or sprue-like enteropathy in any patients. (Dr. Turner Dep. Tr., 57:9-15; Ex. 1 to the accompanying Certification of Adam M. Slater). Dr. Turner acknowledges that physicians at some of the "top celiac centers in the United States" have diagnosed patients with sprue-like enteropathy caused by Olmesartan. (Dr. Turner Dep. Tr., 84:8-85:2.). He admits the strong analogy to celiac disease, and that one of those celiac specialists, Dr. Joseph Murray, an author of the Rubio Tapia study, the seminal article

on OAE, and other important articles on the subject, is "considered the or one of the most respected celiac specialists in the world," and is indeed the, "world's authority regarding celiac disease." (Dr. Turner Dep. Tr., 24:9-23, 145:14-146:6). Curiously, Dr. Turner has no opinion on, "whether there's a class effect for ARB's inducing enteropathy." (Dr. Turner Dep. Tr., 132:5-8).

2. Dr. Turner's Lack of Experience and Knowledge

Dr. Turner's opinion disagreeing with the scientific consensus is not based on any directly relevant knowledge or experience, because he has no experience with the evaluation of any Olmesartan patients in a clinical context outside of this litigation. (Dr. Turner Dep. Tr., 29:10-14, 130:19-131:1). Dr. Turner is a pathologist who spends most of his time on research, spending 8 weeks per year looking at biopsies. (Dr. Turner Dep. Tr., 26:19-24, 27:2-12). The first time that he ever looked at a biopsy for a patient where OAE was a part of a differential diagnosis was in connection with this litigation. (Dr. Turner Dep. Tr., 28:11-15). Indeed, before being contacted by defense counsel in February 2016, he had never conducted any studies of Olmesartan, never published any articles regarding Olmesartan, never given any presentations on Olmesartan, and had no involvement in any research regarding Olmesartan. The most he could say was that he knew some articles had been published, but he could not identify any other than the 2012 Rubio-Tapia article. (Dr. Turner Dep. Tr., 23:17-24:8, 25:6-16).

3. Dr. Turner Applied No Reliable Methodology

Dr. Turner did not identify any scientific methodology in his report. For example, he does not reference the Bradford Hill criteria in his report or in his deposition. (Dr. Turner Report; Slater Cert., Exhibit. 2). Instead, Dr. Turner goes study by study, applying his own test – if the study was not randomized and controlled it cannot establish causation by definition (see below). Since

he knows that there are no adequately powered studies that meet that criteria, his made up causation test assures the outcome.

4. Dr. Turner Reviewed Virtually No Daiichi Documents.

Dr. Turner was provided less than five Medwatch reports and two internal Daiichi reports, one regarding Olmesartan/celiac disease MedWatch adverse event reports, and the other Olmesartan/SLE adverse event reports, days before his deposition, long after he authored his report. He did not see any other Daiichi documents, the depositions of the Daiichi employees who authored the reports, or any other employees' depositions. (Dr. Turner Dep. Tr., 41:17-43:5). Dr. Turner testified that the MedWatch reports he saw were significant, "and showed correlation," which he defined as follows: "Correlation means if something, A, happened, then more often than not B will follow or be accompanying that." He agreed the reports, "did show a correlation between olmesartan and gastrointestinal illness…in some individual cases…" (Dr. Turner Dep. Tr., 48:20-49:17). However, he was not shown any such reports where an internal Daiichi physician performed a causality assessment." (Dr. Turner Dep. Tr., 49:18-22). Dr. Turner acknowledged that if there were MedWatch reports in which Daiichi found a gastrointestinal condition, "was definitely related to the use of olmesartan….those would be worth seeing." Daiichi did not provide or describe such reports to him. (Dr. Turner Dep. Tr., 49:23-51:4).[1]

Dr. Turner did not see any Daiichi internal documents where Daiichi's internal physicians reviewed adverse event reports and concluded that Olmesartan caused the symptoms. He admitted that would be "very significant," to him, and, depending on the data, that could change his opinions. (Dr. Turner Dep. Tr., 94:21-95:12).

5. Dr. Turner Applied an Unreasonably High Personal Standard.

[1] Dr. Turner did not produce and could not identify the MedWatch reports he saw. (Dr. Turner Dep. Tr., 51:16-23).

Dr. Turner applied an unreasonably high standard, personal to him, to determine causation, setting the bar so high that relevant, admissible evidence would not be objectively factored into the analysis. He is so eager to deny causation that he stated, when questioned by defense counsel, that one would need a randomized trial to prove causation in an individual case, with no reference to differential diagnosis. (Dr. Turner Dep. Tr., 304:17-305:24).

In questioning about the Rubio-Tapia article (Slater Cert., Exhibit 3), specifically Table 3 titled: "Clinical Features of Spruelike Enteropathy Associated With Olmesartan," he disagreed with Dr. Joseph Murray and his co-authors from the Mayo Clinic that if a patient meets those criteria, an association is shown. (Dr. Turner Dep. Tr., 69:20-70:7). He testified that to see an association, one would need to see a **controlled rechallenge or highly controlled dechallenge**. (Dr. Turner Dep. Tr., 73:19-74:12). Dr. Turner testified that he will only agree causation is proven by a study demonstrating "a **controlled and properly done, blinded rechallenge.**" (Dr. Turner Dep. Tr., 118:20-120:17). **However, he also admitted that there is no peer-reviewed article that adopts or even approves of that methodology**. (Dr. Turner Dep. Tr., 121:9-18). While Dr. Turner requires a randomized controlled study to establish causation, he admits he does not know "how many patients you'd need," nor how much that study would cost, or address the ethical issues involved in rechallenging a patient with a life-threatening condition.[2] (Turner Dep. Tr., 216:6- 217: 6).

This approach led Dr. Turner to exclude important data that strongly supports causation. He agreed that several important data points weighed in favor of causation, but used his

[2] Indeed, the Rubio-Tapia peer-reviewed publication addresses this ethical issue: "No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and reintroduction of olmesartan." Rubio-Tapia, et. al., *Severe Sprue like Enteropathy Associated with Olmesartan*, Mayo Clin. Proc. Aug. 2012, at 735. (Slater Cert., Exhibit 3)

"randomized controlled study" test to preclude agreement that there is causation. For example, he agreed in the context of questioning about the FDA's identification of 23 OIE cases, with 10 having positive rechallenges, that, "the positive dechallenges and positive rechallenges reported in the literature, they all weigh on the side of supporting the opinion that olmesartan causes this condition." (Dr. Turner Dep. Tr., 123:9-124:16). With regard to the 10 patients with positive rechallenges referenced above, he agreed, "Yes, that would be on the in favor of causation side of the balance." (Dr. Turner Dep. Tr. 124:20-126:7). In this context, the 10 rechallenges were referenced in an article co-authored by Dr. Murray from the Mayo Clinic, who he agreed is a world authority on celiac disease and has published more articles, "regarding the clinical manifestations and treatment of olmesartan-associated enteropathy," than anybody else, titled, "Drug-Induced Enteropathy," (Slater Cert., Exhibit 4) which Dr. Turner agreed is synonymous with "caused by." (Dr. Turner Dep. Tr., 125:13-127:4). Dr. Murray and his co-authors state that Olmesartan is a drug "capable of increasing inflammation in some individuals and, if not recognized, can lead to chronic diarrhea," but Dr. Turner arbitrarily disagrees with this world renowned expert, based on the "Turner test." (Dr. Turner Dep. Tr., 128:7-17). Yet, because "these reports exist," Dr. Turner agrees it is reasonable for doctors to consider Olmesartan in the differential, and to keep the patient off the drug if the symptoms resolve, based on consideration of cause and effect. (Dr. Turner Dep. Tr. 132:23-134:1). He also agreed that based on the clinical information described in the Rubio-Tapia article, "Retrospectively, you would include something related to olmesartan as a possible cause, yes." (Dr. Turner Dep. Tr., 142:5-143:24). Even though case reports can reasonably inform clinical findings of causation, they "can't prove causation." (Dr. Turner Dep. Tr., 215:4-216:5). This is one of the central logical breaks in the methodology, unmasking it as a tool to deny causation regardless of all other evidence.

When discussing the Cartee article, (Slater Cert., Exhibit 5) he agreed that it would seem reasonable to "hold Olmesartan much earlier in the natural history of the illness rather than assuming another diagnosis first in order to limit worsened symptoms." (Dr. Turner Dep. Tr., 223:9-224:9). He also agreed that "where all of those symptoms [referring to OAE] resolved after the drug is discontinued, that fits the diagnostic criteria for" OAE. (Dr. Turner Dep. Tr., 227:4-10). Inexplicably, he contradicts this entire analysis, opining that there is not one reliable diagnosis of OIE in the literature since none, "met scientific rigor of causation." (Dr. Turner Dep. Tr., 214:10-215:3).

6. Dr. Turner Relied on Underpowered Studies to Deny Causation.

Dr. Turner is not an epidemiologist and testified he does not plan to provide epidemiologic opinions in this litigation. (Dr. Turner Dep. Tr., 254:9-10; 254:9-12.). In his report, he relied in part on what he termed negative findings in particular studies. However, at his deposition he conceded that the studies were not adequately powered to answer the causation question.

Dr. Turner did not perform power calculations to determine whether the ROADMAP study was sufficiently powered to look for OAE because he lacked the epidemiological experience to conclude whether the ROADMAP study was sufficiently powered to study adverse events, and said he has no opinion on that question, but agreed that if it is underpowered (as admitted by Daiichi) it will not yield reliable information on that question. (Dr. Turner Dep. Tr., 182:20-184:12.). He also agreed that the diabetic population of the ROADMAP study was not representative of patients taking Olmesartan on the whole since they are not all diabetic, and taken together with the fact that the study was not designed to study the question, and was underpowered to study the question, it does not answer the question of whether or not there is an association. (Dr. Turner Dep. Tr., 202:18-203:17).

He was also unaware of causality assessments on patients in the Olmesartan arm of the ROADMAP study, including a patient who "developed gastroenteritis, vomiting, and diarrhea so severe that she was hospitalized. When she went off olmesartan, she got better. When she went back on it, she got sick again." The causality assessment for the, "hospitalization because of gastroenteritis," was "probably related." (Jeffrey Warmke Dep. Tr., 327:21-334:24; Slater Cert., Exhibit 6). Another ROADMAP causality assessment determined that a ROADMAP patient's collagenous colitis was definitely related to Olmesartan. (Jeffrey Warmke Dep. Tr., 347:15-350:10; Slater Cert., Exhibit 6). Dr. Turner stated that if a causality assessment were performed and showed the adverse event was caused by Olmesartan he would want to see it, but that was never provided to him. (Dr. Turner Dep. Tr., 49:18-50:13).

Dr. Turner also admitted that the Greywoode, study, (Slater Cert., Exhibit 7), "probably wasn't sufficiently powered." (Dr. Turner Dep. Tr., 254:14-255:13). He also agreed that the Lagana study, (Slater Cert., Exhibit 8) also had a small sample size that was a limitation as well. (Dr. Turner Dep. Tr., 242:10-243:18). Dr. Turner's reliance on underpowered studies to support his opinion that causation is not statistically demonstrated is a flaw in his method.

7. Dr. Turner's Unscientific Rejection of Basson.

Dr. Turner rejected the Basson epidemiological study of the French National Health Insurance database, which studied the rate of hospitalizations for malabsorption, comparing patients on Olmesartan to patients on other anti-hypertensive medications. The study showed an "adjusted rate ratio of hospitalization with a discharge diagnosis of intestinal malabsorption was 2.49 for olmesartan users…and 10.65…beyond 2 years of exposure," and concluded that, "Olmesartan is associated with an increased risk of hospitalization for intestinal malabsorption and celiac disease." (Slater Cert., Exhibit 9). Dr. Turner's rejection of the findings in the largest body

of patient years studied is a classic diversion, because he criticized the study in his report for being a "retrospective analysis based solely on patient coding, which is not entirely reliable." (Dr. Turner Report at 6). Since that is an aspect of how this type of data is always compiled, and he has no idea how the coding was performed, the criticism is unfounded.

8. Dr. Turner Admits that Mechanism is Not a Basis to Deny Causation.

Dr. Turner did agree that if Plaintiffs' experts, and the peer reviewed literature are correct that the mechanism for OIE is "an immune mediated response that causes cellular changes that leads to inflammation and villous atrophy, and then the symptoms that are seen with this condition," then "it would be a plausible biological mechanism, absolutely." (Dr. Turner Dep. Tr., 233:13-234:2). He also agreed that causation can be established with enteropathy without the need to know the precise mechanism for causation, in the context of NSAIDS. (Dr. Turner Dep. Tr., 136:14-141:10).

9. Dr. Turner's Admissions of Association and Causation.

Dr. Turner agreed that there is a spectrum of association, from chance associations at one end to causal associations at the other. (Dr. Turner Dep. Tr., 64:15-19). Notably, Dr. Turner acknowledged that the FDA's July 3, 2013 Drug Safety Communication (Slater Cert., Exhibit 10) said Olmesartan, "can cause intestinal problems known as sprue-like enteropathy," and in a slip of reason stated that he does not "disagree with the FDA." (Dr. Turner Dep. Tr., 98:16-99:2). Dr. Turner also agreed that if a patient's symptoms were to recur with a controlled rechallenge in a randomized controlled trial, "that is strong evidence of causation." (Dr. Turner Dep. Tr., 100:14-19). As set forth above, Dr. Turner was not shown the MedWatch report from the ROADMAP patient who had a positive dechallenge, then rechallenge, then another dechallenge, but based on Dr. Turner's test, that report is strong evidence of causation, which he did not factor in.

Dr. Turner agrees it is possible Olmesartan can cause sprue-like enteropathy, but just wants to see more rigorous studies to prove it. (Dr. Turner Dep Tr., 279:9-23). In questioning about a page on the website of the hospital employing Dr. Turner, Brigham & Women's Hospital, indicating side effects one may "notice from receiving" Olmesartan, including diarrhea, vomiting, and weight loss, he agreed it is "possible" those are side effects "that a patient may experience from receiving olmesartan." (Dr. Turner Dep. Tr., 87:10-88:22).

Dr. Turner admitted that positive dechallenges and rechallenges reported in the literature weigh on the side of support for the proposition that Olmesartan causes enteropathy. (Dr. Turner Dep. Tr. at 124:8-16). Dr. Turner admits that where all the symptoms are resolved after the drug is discontinued, that this fits the diagnostic criteria of the condition, as described. (Dr. Turner Dep. Tr., 227:4-10).

In discussing the Kulai case report (Slater Cert., Exhibit 11), he agreed that based on the description in the report Olmesartan was the most likely cause of the patient's symptoms including severe diarrhea, vomiting, and a 20 pound weight loss. (Dr. Turner Dep. Tr., 287:17-288:7, 296:1-10).

10. Dr. Turner Admitted It is Reasonable for Clinicians to Find Causation.

Dr. Turner was asked if the existing studies are sufficient for doctors "to know what this entity is as described, and to use that information to treat their patients," and confirmed:

> I think they have enough information to be aware of it as a possible entity, and if their patient – and to do a therapeutic trial by withdrawing the medication. If their patient does well, then they shouldn't put the patient back on olmesartan because there are plenty of alternatives, and they don't need more information for patient management.

(Dr. Turner Dep. Tr., 300:12-301:7). He then agreed:

> So the state of the scientific literature is sufficient to provide the physicians who actually have to treat patients in this area with the information they need to treat the patients.

(Dr. Turner Dep. Tr., 301:8-13).

Dr. Turner also cited a case report in the form of a letter from Doctors Gallivan and Brown to the editor of a journal presenting a case report (Slater Cert., Exhibit 12) regarding a woman who "experienced severe watery diarrhea which resulted in three hospital admissions, including an ICU admission for acute renal failure secondary to dehydration," with villous blunting, negative celiac tests, and had positive dechallenge, then rechallenge, then another positive dechallenge with improvement of the villous blunting, when she was taken off Olmesartan for good. The authors of this peer-reviewed case report recommend: "Thus, it is important to consider **olmesartan induced enteropathy** in patients with histological sprue-like findings, with or without colonic inflammation, in the absence of other celiac disease or other medical condition." Dr Turner agreed it would be "reasonable to permanently withdraw the olmesartan," because "of the possibility that the olmesartan was causing the clinical syndrome." Finally, he agreed that the resolution of the symptoms and normalization of the pathology establishes, "a correlation," and praised the decision to withdraw the Olmesartan as, "a good management decision in the patient." Yet, he would not agree to the word "cause," arguing, "I'm saying we need a controlled and properly done randomized rechallenge, and then you can make a determination about one patient." (Dr. Turner Dep. Tr., 104:7-107:9, 111:12-114:15, 115:16-119:17). Of particular note, he did analyze the pictures of the histopathology presented in the report in the course of the cited testimony, and in agreeing he saw improvement stated, "With the recognition that **celiac-like diseases** are patchy, yes." Of course, the celiac-like disease he referenced is OIE – the condition the authors identified for this patient.

I.

THE DAUBERT STANDARD

The admissibility of expert testimony is determined in Federal Court pursuant to Federal Rule of Evidence 702. The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. Padillas v. Stork-Gamco, Inc., 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of science, rather than on subjective belief or unsupported speculation." In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting Daubert, 509 U.S. at 590). These good grounds must support each step of the analysis and "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." Id. at 745. Judges within this Circuit also consider how and when the methodology is used outside of litigation. Paoli, 35 F.3d at 742 (discussing reliability factors under Daubert and Third Circuit case law).

Furthermore, " 'Daubert's gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" Elcock v. Kmart Corp., 233 F.3d 734, 746 (3d Cir.2000) (quoting Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999)); see also Magistrini v. One Hour Martinizing Dry Cleaning, 180 F.Supp.2d 584, 594 (D.N.J.2002), aff'd, 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the litigation (*see* Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir. 1995)); (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion (see General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118

> S.Ct. 512, 139 L.Ed.2d 508 (1997)); (iii) whether the expert has adequately accounted for alternative explanations (see Claar v. Burlington, N.R.R., 29 F.3d 499 (9th Cir. 1994)).

Magistrini, 180 F. Supp. 2d at 594–95. Dr. Turner fails all three tests.

II.

DR. TURNER'S OPINION ON GENERAL CAUSATION SHOULD BE PRECLUDED PURSUANT TO DAUBERT

In essence, Dr. Turner offers a personal opinion driven entirely by litigation, based on no true methodology, which willfully ignores and directly contradicts the prevailing scientific consensus, and fails to factor in or account for significant evidence supporting causation. In granting a motion to preclude an expert under Daubert, this Court has observed:

> [C]ourts also need not admit mere conclusions or opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered…. Mere assumptions, without causal evidence or methodological analysis may be inadmissible . . . . Conclusions based only on the expert's experience, and testimony founded on methods that are not generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard. Furthermore, conclusions based on analogies that are too dissimilar to the subject of the testimony may also merit exclusion.

Player v. Motiva Enterprises LLC, 2006 WL 166452, at *6-7 (D.N.J. January 20, 2006) (citations omitted). In Player, this Court found the expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, relied on, "a highly misleading analogy," and relied on a scientifically unsound survey. Id. at *7. The court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any real standards." Id. at *8.

Dr. Turner was barely aware of the existence and had no personal knowledge or experience regarding OIE/OAE until he was hired as a defense expert. This lack of knowledge and experience should result in greater scrutiny of the method actually applied by the expert. See Elcock, 233 F.3d at 747 (quoting Paoli, 35 F.3d at 742, n. 8). In addition, Dr. Turner is offering a rogue opinion that is directly inconsistent with the prevailing scientific consensus, thus the method that yielded that opinion should be scrutinized quite closely. See In re Zoloft Products Liability Litigation, 176 F. Supp. 3d 449, 460-61 (E.D. Pa. 2016) (citing In re Rezulin Products Liability Litigation, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) ("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable.")).

1. Reliability of Opinion.

Dr. Turner's method can be summarized as a review of the literature listed in his report, his opinion on the strength of the literature, and whether from this review he believes there is an association or a causal relationship shown by those studies. (*See generally* Turner Report). In order for his opinions to be admissible, "the process or technique used in formulating the opinion [must be] . . . reliable," and the principles and methods employed by the expert [must be] . . . applied reliably to the facts of the case. Pineda, 520 F.3d at 247 (citing Paoli, 35 F.3d at 742); see also Fed. R. Evid. 702, Advisory Committee's Note.

Dr. Turner formed his opinions in this case solely for the purposes of litigation. He has never performed research or thought about Olmesartan outside this litgation. This should factor into the Court's determination of reliability:

> One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. That an expert testifies for money

> does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir.1995). Expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert's line of scientific research or technical work should be viewed with some caution. Magistrini, 180 F. Supp. 2d at 594 (D.N.J.2002) (finding that where an expert formed opinions solely for purposes of litigation that is a factor courts consider in determining reliability). Since Dr. Turner has no professional experience outside of this case related to OAE, the process by which he arbitrarily selected and neglected data to educate himself on this subject is critical.

2. Dr. Turner Conducted an Internally inconsistent, One-sided Analysis of the Evidence in Absence of any Stated Methodology.

Dr. Turner engages in an inconsistent and biased analysis. In the absence of any stated methodology, he agrees the evidence that supports causation deserves weight but then refuses to rely on the evidence if it is not from a randomized controlled trial setting, but then remains wholly unaware of the fact that such adverse event evidence exists but was not given to him.

An expert's opinion is unreliable if the expert does not disclose the methodological systematic process upon which his opinions were based. Indeed, in order to ensure that the methodology is truly a methodology, rather than a mere conclusion-oriented selection process, there must be a scientific method that is used and explained. Magistrini, 180 F. Supp. 2d at 607. An expert's failure to comment on the potential weaknesses of the studies upon which an expert relies nor to acceptably explain why he did not accord more weight to other studies that did not align with his conclusions renders the opinion unreliable. Magistrini, 180 F. Supp. 2d at 584. Dr. Turner violated these requirements.

a. Dr. Turner Applied an Unreasonably High Standard to the Literature Supporting Causation.

Dr. Turner applied an unreasonably high standard to the literature that supports causation. He set the bar so high that relevant, admissible evidence could not be objectively factored into the analysis. For example, Dr. Turner's methodology led him to conclude that no documented dechallenges and rechallenges in the literature are scientifically valid. The refusal to consider scientific evidence that does not involve a randomized controlled trial is not supported in law, especially considering the significant number of observational epidemiological studies published on OIE. Nothing requires the evidence to take the form of, or to be comprised even in part, of randomized controlled studies. See e.g., Terry v. McNeil-PPC, Inc. (In re Tylenol (Acetominophen) Mktg., 198 F. Supp. 3d 446, 456-60 (E.D. Pa. 2016) (rejecting defendants' argument that plaintiff expert's opinions are unreliable because there is no epidemiological or case-controlled studies available, finding that such studies are not feasible and/or too expensive to conduct for a rare side effect); In re Asbestos Litig., 911 A.2d 1176 (Del. Super. Ct. 2006) (finding that Plaintiffs need not support their general causation case with epidemiological evidence as a matter of law"); In re Avandia Mktg., 2011 U.S. Dist. LEXIS 479, at *21-22, 44-45 (E.D. Pa. Jan. 3, 2011) (finding plaintiff expert's testimony reliable even without RCT evidence because they used the same studies and evidence as the Defendants as well as the FDA in their evaluation of the risk profile of the drug Avandia) (further noting that a disadvantage of RCTs is "because of the cost and complexity of conducting them, they are often inadequate in size to truly address the risk of serious but uncommon outcomes"); In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig., 26 F. Supp. 3d 449, 453 (E.D. Pa. 2014) (noting that RCTs may not be ethically conducted in the context of the drug's side effects and patient population).

Dr. Turner's test is simply an outcome driven tool to allow him to reject the overwhelming consensus in the literature and medical community, joined by the FDA, confirming general causation. As demonstrated, this strategy to try to invalidate virtually every source of data and every peer reviewed conclusion, is inconsistent with the law and should be rejected.

CONCLUSION

For the foregoing reasons, Dr. Turner should be precluded from offering his opinion denying general causation.

Respectfully,

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